

Reconsideration of the application in view of the following remarks is respectfully requested.

REMARKS

A. Status of the Claims

Claims 1-18 were examined and remain pending. No amendments or cancellations have been made. A clean copy of the pending claims is attached for the Office's convenience at Appendix 1.

B. The Claims Are Enabled

The Office rejects claims 1-18 under 35 U.S.C. § 112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention[.]" November 2002 Office Action at p. 2. Applicants respectfully traverse.

1. Claim 1

Claim 1 includes "accessing data representing a multiple sequence alignment (MSA) of a plurality of polymer sequences." Claim 1 also includes identifying one or more positions in the MSA that have statistically significant conservation energy values using the recited equation.

a. "accessing data"

The Office questions how this step occurs. For example, the Office asks, "what polymers are selected, on what basis are they selected, and how are they aligned in a multiple sequence alignment?" Action at p. 3.

Applicants are not claiming the creation of an MSA. Instead, Applicants are claiming accessing **existing** data representing an MSA of a plurality of polymer sequences. Nevertheless, even were Applicants claiming the creation of an MSA, such a step would be enabled.

For example, the Background of the specification references examples of texts that involve the creation and use of MSAs. Furthermore, volume 266 of *Methods in Enzymology* (©1996) entitled “Computer Methods in Macromolecular Sequence Analysis” is dedicated to the process of creating MSAs and to the application of prior established methods operating on MSAs. Section III of this work, entitled “Multiple Alignment and Phylogenetic Trees,” is attached as exhibit A to the Declaration of Rama Ranganathan (Ranganathan Declaration). This section addresses MSAs of polymers sequences such as proteins and DNA. Other works that address protein MSAs include “Gapped BLAST and PSI-BLAST: a new generation of protein database search programs” by Altschul *et al.*, *Nucleic Acids Research*, 1997, Vol. 25, No. 17, pgs. 3389-3402 (ex. B); and “SCOP: a Structural Classification of Proteins database” by Hubbard *et al.*, *Nucleic Acids Research*, 1999, Vol. 27, No. 1, pgs. 254-256 (ex. C). Works that address RNA MSAs include “The Ribonuclease P Database” by Brown, *Nucleic Acids Research*, 1999, Vol. 27, No. 1, pg. 314 (ex. D); “tRNAscan-SE: a program for improved detection of transfer RNA genes in genomic sequence” by Lowe *et al.*, *Nucleic Acids Research*, 1997, Vol. 25, No. 5, pgs. 955-964 (ex. E); “Conservation of functional features of U6atac and U12 snRNAs between veterbrates and higher plants” by Shukla *et al.*, *RNA* (1999), 5:525-538 (ex. F); and “The uRNA database” by Zwieb, *Nucleic Acids Research*, 1997, Vol. 25, No. 1, pgs. 102-103 (ex. G). [Ranganathan Declaration at ¶¶ 6-7].

Methods discussed in volume 266 of *Methods in Enzymology* have been fundamental to a recognition of sequence homology as implemented in the BLAST® family of search tools, many of which – including versions of BLAST and PSI-BLAST (which also actually create alignments) – have existed in the art for more than 6 years; to the creation of phylogenetic trees

since prior to October 6, 1999; and have been routine in the practice of molecular biology for guiding experimentation since prior to October 6, 1999. [Ranganathan Declaration at ¶ 8].

Alignment methods are introduced in the required coursework for many biology graduate students, and have been since prior to October 6, 1999. [*Id.* at ¶ 9]. Interactive practical education in advanced methods have also been routine for upper-level bioinformatics graduate students since prior to October 6, 1999. [*Id.* at ¶ 10]. The specification itself describes how certain protein sequences were aligned on pages 25 and 26.

For at least these reasons, the skill required to create MSAs that may be accessed consistent with the “accessing” step of claim 1 is no greater than that which is the standard of practice in the bioinformatics community. [*Id.* at ¶ 11].

The Office also questions the types of polymers in addition to proteins that are amenable to the claimed methods:

The specification, at page 6, indicates that proteins are polymers that can be used, but is silent to other polymers amenable to the method. For instance, are polyacrylamide polymers able to be used in this method? How would such non-protein polymers be aligned? Could free energy calculations be performed?

Action at p. 3. In fact, the specification **does teach that other polymers are amenable to use with the claimed methods:**

The inventive methods may be used to analyze biological sequences other than proteins. For example, ΔG_{stat} and $\Delta \Delta G_{i,j}^{\text{stat}}$ may be calculated for polysaccharides, lipids, deoxyribonucleic acid (DNA, represented by A, C, G, and T bases), and ribonucleic acid sequences (RNA, represented by A, C, G, and U bases) to identify evolutionary conservation and interacting pairs of components. Any polymer of monomers may be analyzed with the inventive methods. Application of the inventive methods is not limited to biological sequences, as it may be applied to chemical polymers, drugs, and other compounds.

Page 29, line 25 – page 30, line 2. “[I]t is incumbent upon the Patent Office . . . to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested

statement.” *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971). The Office, however, has provided no such reasoning or evidence.

b. “identifying one or more positions”

In addition to “accessing data,” claim 1 recites:

- (b) identifying one or more positions within the MSA that have statistically significant conservation energy values using the following equation:

$$\Delta G_i^{stat} = kT^* \sqrt{\sum_x \left(\ln \frac{P_i^x}{P_{MSA}^x} \right)^2}$$

wherein:

i is a position in the MSA;

ΔG_i^{stat} is the conservation energy value for position i ;

P_i^x is the probability of monomer x at position i ;

P_{MSA}^x is the probability of monomer x in the MSA; and

kT^* is an energy unit, where k is Boltzmann’s constant.

Thus, Applicants have claimed the identification of one or more positions with statistically significant conservation energy values, including an algorithm for arriving at conservation energy values.

In judging enablement, this step must be read in conjunction with the specification, which includes an explanation of how to calculate conservation energy values using the claimed equation on pages 18 and 19 of the specification. The specification also includes an exemplary manner of arriving at “statistically significant conservation energy values”:

“Statistically significant conservation energy values” may vary with the application. In general, this refers to values that are greater than the background “noise” value. **One manner of arriving at values that are greater than the background noise is to fit the set of energy values for all positions in an alignment to well-established Gaussian error models. Values greater than two standard deviations from the mean may be classified as “statistically significant.”**

Page 17, lines 14-19 (emphasis added). Further, Applicants provide an example on page 26 of the specification that involved the use of the claimed equation in identifying one or more positions with statistically significant conservation energy values. Lines 14-24 (“For example, the groove on the surface of the PDZ domain that contains the co-crystallized peptide ligand emerges as the most conserved portion of the protein family.”). Claim 1 is enabled based at least on these teachings.

i. refutation of Office’s arguments

The Office makes a number of statements that lack factual or legal support. Applicants address them in the order they appear.

(a) “critical steps”

The Office begins its analysis by asserting that the claims and specification lack “critical steps and information required for the performance” of the claimed methods. The Office does not point to the steps that it believes are critical, nor the basis on which it deems them critical. Moreover, Applicants do not characterize any step as “critical” in the specification. Accordingly, if the alleged omission of a “critical” limitation is the basis for the Office’s enablement rejection, the Office has not met its burden. *See* M.P.E.P. § 2164.08(c) at p. 2100-189 (August 2001) (“Therefore, an enablement rejection based on the grounds that a disclosed critical limitation is missing from a claim should be made only when the language of the specification makes it clear that the limitation is critical for the invention to function as intended.”).

(b) “concrete active step(s)”

The Office also states:

Once the polymer sequences are chosen and defined, it is unclear how the simple act of calculating the free energy of each position means anything without any

cross comparison of free energy values between similar positions of other proteins in the family. A calculated value on its own, with no reference or baseline value tells one nothing of significance. The claims do not have any such steps wherein values are compared and significance concretely defined and gained. The “identifying” step in claims 1 and 10 is devoid of any concrete active step(s) such that one of skill in the art would be able to follow such a step.

Action at p. 4. Applicants have not claimed the “simple act of calculating the free energy of each position,” as the Office asserts. Instead, as set forth above, Applicants claim the identification of one or more positions within the MSA that have statistically significant conservation energy values using an equation that gives the conservation energy value of positions within the MSA. The claimed step of identifying, however, **is not limited to** performance of **only** that equation, as the Office seems to assert.

The claimed step of identifying must be read in conjunction with the specification of which it is a part. Claim 1 is clearly enabled when this is done. For example, as explained above, Applicants have provided an example of how to arrive at “statistically significant conservation energy values” on page 17 of the specification. Applicants have also provided an explanation of how to calculate conservation energy values using the claimed equation on pages 18 and 19 of the specification. Further, Applicants provide an example on page 26 of the specification that involved the use of the claimed equation in identifying one or more positions with statistically significant conservation energy values. Lines 14-24 (“For example, the groove on the surface of the PDZ domain that contains the co-crystallized peptide ligand emerges as the most conserved portion of the protein family.”).

The Office appears to want Applicants to incorporate the relevant teachings from the specification into the claims at issue. For example, the Office states, “[t]he ‘identifying’ step in claims 1 and 10 is devoid of any concrete active step(s) such that one of skill in the art would be able to follow such a step.” It is not, however, necessary for Applicants to so limit the claims

when the prior art does not necessitate it. *See* M.P.E.P. § 2164.08(c) at p. 2100-189 (“Limiting an applicant to the preferred materials in the absence of limiting prior art would not serve the constitutional purpose of promoting the progress in the useful arts.”). Moreover, limiting the claims in such a fashion is not, and cannot be, the standard. Otherwise, there would be no need for a specification. The claims recite accessing certain data and identifying certain information concerning that data using an explicit equation. The claims need no more information to be enabled.

(c) direction and working examples

In analyzing the *Wand* factors, the Office mischaracterizes the amount of direction provided by the inventors and the existence of working examples. Specifically, with respect to these factors, the Office states:

The specification provides working examples of using the particular method to calculate free energy for PDZ domains (page 26 and 27) that are known to be a family of small, evolutionarily well-represented protein binding motifs (page 25). The energetic profile of the fold family was determined and the energetic coupling function was determined. **No specific steps to do this are outlined in the examples.**

Action at pp. 4-5. (emphasis added). The Office’s statement ignores the specification’s teaching about how data representing an MSA of a plurality of polymer sequences may be accessed (*see, e.g.*, page 5, lines 12-15; page 5, lines 21-27; page 6, lines 1-4; page 6, lines 6-8; and page 20, lines 13-18; and page 25, line 20 – page 26, line 4); how to obtain conservation energy values of positions within an MSA (*see, e.g.*, page 18, line 4 – page 19, line 11; page 20, line 20 – page 21, line 18; page 23, line 5 – page 24, line 4; and pages 41-53); and how to identify statistically significant conservation energy values from among the conservation energy values computed (*see, e.g.*, page 17, lines 14-19; page 21, lines 20-28; page 26, lines 14-24).

Furthermore, the Office's characterization of the working examples is not complete. The specification includes an example of how to develop an overall energetic profile for a fold family (Example 3), which involves performance of the accessing and identifying functions of claim 1. Contrary to the assertion of the Office, the example and relevant teachings **do include** specific steps. For example, the polymers selected for use in the MSA were identified in these portions of the specification. The example explains that the initial alignment was created using PILEUP and certain manual techniques. The example also states that "[e]quation 4 was used to calculate ΔG^{stat} for all positions on the PDZ domain alignments." Using the results of that calculation, the example explains that "the groove on the surface of the PDZ domain that contains the co-crystallized peptide ligand emerge[d] as the most conserved portion of the protein family." Specification at p. 26, lines 14-24.

The specification also includes an example (Example 4) of what amino acids were energetically coupled to PDZ position 76 from the MSA created as outlined in Example 3. This example involved performance of the same accessing step performed as outlined in Example 3. This example also involved performance of the identifying step of claim 1 because the equation taught (equation 5 in the specification) is two calculations using the claimed algorithm that have been subtracted from each other. Thus, at least the claimed equation was used. The identification of the amino acids that were energetically coupled to PDZ position 76 was confirmed through thermodynamic mutant cycle analysis, as set forth in Example 5.

(d) the nature of the invention

The Office characterizes the nature of the invention as being "drawn to multiple sequence alignments to identify free energy and significant positions." Action at p. 5. The invention defined by claim 1 is directed to accessing data representing an MSA of a plurality of polymer

sequences; and identifying one or more positions within the MSA that have statistically significant conservation energy values using a recited equation. The invention defined by claim 10 is directed to accessing data representing an MSA of a plurality of polymer sequences; calculating a conservation energy value for each position in the MSA using a recited equation; and identifying one or more positions within the MSA that have statistically significant conservation energy values.

* * *

Claim 1 and its dependent claims are enabled. There is ample support in the specification for manners in which statistically significant conservation energy values may be identified using the recited equation. The Office's only "evidence" to the contrary are unsupported assertions that are inconsistent with the specification.

2. Claims 4 and 13

The Office asserts that "it is further unclear where in the methods of claim 1 and 10 the graphing should take place. Does this occur before or after the identification of the position?" Action at p. 4. Applicants submit that this query does not satisfy the Office's burden when making an enablement rejection. Moreover, "[u]nless the steps of a method actually recite an order, the steps are not ordinarily construed to require one." *Interactive Gift Express, Inc. v. CompuServe Inc.*, 256 F.3d 1323, 1342-43, 59 USPQ2d 1401, 1416 (Fed. Cir. 2000). To facilitate examination, however, Applicants note that the specification teaches that graphing may take place after conservation energy values are calculated. *See, e.g.*, specification at page 26, lines 14-16. For at least this reason, claims 4 and 13 are enabled.

3. Claims 7-9 and 16-18

The Office asserts that these claims require accessing data, but “claims 1 and 10 do not require the acquisition and/or storage of any polymer data. It is unclear if only sequence data is needed or required or whether free energy data or some other types of data are utilized. The specification does not clearly address this issue. The specification indicates that data can come from a variety of sources, but no particular type of format is required such that one of skill in the art would be able to obtain or provide such data.” Action at p. 4.

The Office’s rejection of these claims is not understood. Both claims 1 and 10 require “accessing data representing a multiple sequence alignment (MSA) of a plurality of polymer sequences[.]” Claims 7-9, which depend from claim 1, and claims 16-18, which depend from claim 10, specify that “the data accessed comprises data from” certain specific domain families. Considering that the step of identifying in claim 1 and the step of calculating in claim 10 concern the same equation – **which pertains to the claimed MSA** – it is clear that “sequence data,” as the Office puts it, may be “utilized.” It is also clear that these claims are enabled in light of the examples and teaching of the specification, discussed in detail above and below.

4. Claim 10

Claim 10 includes “accessing data representing a multiple sequence alignment (MSA) of a plurality of polymer sequences.” Claim 10 also includes calculating a conservation energy value for each position in the MSA using a recited equation. Claim 10 further includes “identifying one or more positions in the MSA that have statistically significant conservation energy values.”

Claim 10 is enabled for substantially the same reasons as claim 1. Although the two claims differ in scope, the teachings and examples from the specification that are cited above with respect to claim 1 apply with equal force to claim 10.

C. Claims 1-9 Are Definite

The Office rejects claims 1-9 under 35 U.S.C. § 112, second paragraph, as being indefinite. The Office asserts that these claims “omit essential steps.” The Office states, “[t]he method of identifying one or more positions in a polymer family requires identification of the positions in a multiple sequence alignment. However, the steps taken in order to perform the identification portion of step (b) are not stated and it is unclear how this would be accomplished.” Applicants respectfully traverse.

The Office appears to require Applicants to amend the claims to recite a “cookbook” of all the methodology that may be used to carry out a specific embodiment of the claims. This is not required under the second paragraph of 35 U.S.C. § 112. All that is required is that the claims describe subject matter with a reasonable degree of clarity and precision. The claim meets this requirement.

For example, step (b) recites:

- (b) identifying one or more positions within the MSA that have statistically significant conservation energy values using the following equation:

$$\Delta G_i^{stat} = kT^* \sqrt{\sum_x \left(\ln \frac{P_i^x}{P_{MSA}^x} \right)^2}$$

wherein:

i is a position in the MSA;

ΔG_i^{stat} is the conservation energy value for position i;

P_i^x is the probability of monomer x at position i;

P_{MSA}^x is the probability of monomer x in the MSA; and

kT^* is an energy unit, where k is Boltzmann's constant.

Based on this claim step, one of ordinary skill in the art would understand that the recited equation is to be used to calculate conservation energy values, and that one or more positions for which conservation energy values are calculated and that have statistically significant values should be identified. That different approaches may be taken for carrying out this step is irrelevant to an indefiniteness inquiry. Breadth is not indefiniteness. M.P.E.P. §2173.04. Thus, contrary to the Office's statements, Applicants respectfully submit that no essential steps are omitted from the claims.

D. Petition for Extension of Time

Pursuant to 37 C.F.R. § 1.136(a), Applicant petitions for an extension of time of two months up to and including April 5, 2003 (and to April 7, 2003 by virtue of April 5th falling on a Saturday) in which to respond to the Office Action dated November 5, 2002. Pursuant to 37 C.F.R. § 1.16 and 1.17, a check for \$ 205 is enclosed as the process fee for the requested extension. If any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an overpayment be included, the Office is authorized to deduct or credit the appropriate fees from or to Fulbright & Jaworski Deposit Account No.: 50-1212/UTSD:645US/MTG.

E. Conclusion

Applicant respectfully submits that claims 1-18 are in condition for allowance. Should Examiner Clow have any questions, comments, or suggestions relating to this application, she is invited to contact the undersigned attorney at (512) 536-3031.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Mark T. Garrett". The signature is fluid and cursive, with the first name "Mark" being more prominent.

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